research article

Diagnostic accuracy of MRI to evaluate tumour response and residual tumour size after neoadjuvant chemotherapy in breast cancer patients

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Background. The aim, of the study was to estimate the accuracy of magnetic resonance imaging (MRI) in assessing residual disease in breast cancer patients receiving neoadjuvant chemotherapy (NAC) and to identify the clinico-pathological factors that affect the diagnostic accuracy of breast MRI to determine residual tumour size following NAC.

Patients and methods. 91 breast cancer patients undergoing NAC (92 breast lesions) were included in the study. Breast MRI was performed at baseline and after completion of NAC. Treatment response was evaluated by MRI and histopathological examination to investigate the ability of MRI to predict tumour response. Residual tumour size was measured on post-treatment MRI and compared with pathology in 89 lesions. Clinicopathological factors were analyzed to compare MRI-pathologic size differences.

Results. The overall sensitivity, specificity, positive predictive value, negative predictive value, and accuracy for diagnosing invasive residual disease by using MRI were 75.00%, 78.57%, 88.89%, 57.89%, and 76.09% respectively. The Pearson´s correlation coefficient (r) between tumour sizes determined by MRI and pathology was r = 0.648 (p < 0.001). The size discrepancy was significantly lower in cancers with initial MRI size ≤ 5 cm (p = 0.050), in cancers with high tumour grade (p < 0.001), and in patients with hormonal receptor-negative cancer (p = 0.033).

Conclusions. MRI is an accurate tool for evaluating tumour response after NAC. The accuracy of MRI in estimating residual tumour size varies with the baseline MRI tumour size, the tumour grade and the hormonal receptor status.

Key words: breast cancer; MRI; residual tumour; neoadjuvant chemotherapy

Introduction

Neoadjuvant chemotherapy (NAC) has been used in the management of large operable breast tumours with the purpose of modifying the surgical planning and increase the rate of breast conserva-tive surgery (BCS).[1-6] Currently, NAC has been extended to selected patients with early-stage disease to improve the cosmetic outcome of BCS, especially in women with small breast size.[7-9] NAC has proved to be equivalent to postoperative chemotherapy in terms of disease-free and overall surviv-

al.[10-12] However, in the neoadjuvant setting, there is evidence that patients who achieve a pathologic complete response (pCR) in the breast after NAC have a better prognosis than patients with a partial response or non-responders.[6,11,13-15] Based on the different behaviour of each tumour subtype, a molecular classification system identifies subgroups of breast invasive carcinoma patients who are most likely to achieve a pCR.[16]

An accurate imaging assessment of tumour response to NAC may facilitate the surgical planning. Magnetic resonance imaging (MRI) is more accurate and sensitive than conventional methods in assessing residual tumour extent after NAC.[17-23] In addition; there has been a positive correlation between MRI-determined and pathologic residual tumour size.[24-29] However, it is necessary to know the factors affecting the diagnostic accuracy of MRI in breast cancer treated with NAC.

The aims of the present study are to evaluate the diagnostic accuracy of MRI to detect residual disease and to predict the tumour extent in patients with breast cancer receiving NAC, and to identify the factors that influence the accuracy of MRI in predicting residual tumour size.

Patients and methods

Patients and tumour molecular characteristics

A total of 91 patients with invasive breast cancer (92 carcinomas) were included in this institutional retrospective study. All patients were diagnosed by core needle biopsy between October 2006 and June 2013. All patients were treated with NAC followed by surgical treatment and underwent MRI before and after NAC for monitoring tumour response to treatment. Considering the Helsinki Declaration principles, the Institutional Research Ethics Committee approved this study (No. 2015/059).

According to the results of the initial diagnostic biopsy, tumours were classified into 5 molecular subtypes based on immunohistochemical characteristics of breast cancer[30] (hormone receptor status, human epidermal growth factor receptor 2 (HER2) status and level of expression of ki-67). Estrogen receptor (ER) and progesterone receptor (PR) were considered positive if ≥ 10% of tumour cell nuclei stained positive. Hormone receptors (HR) were considered positive when the ER, PR, or both were positive. HER2 tumours scoring 3+ (intense homogeneous membranous staining in ≥ 10% of tumour cells) were considered positive. In case of 2+ scores

(moderate complete membranous staining in ≥ 10% of tumour cells), the technique of fluorescent in situ hybridization was used to determine HER2 gene amplification. Samples with scores 0 to 1+ were considered negative. The cut-off of ki-67 expression level was set at 14%, to determine whether the cell proliferation index was high (> 14%) or low (≤ 14%). The five categories of molecular subtypes were: *luminal A-like* subtype (HR positive, HER2 negative, ki-67 ≤ 14%), *luminal B/HER2-negative-like* subtype (HR positive, HER2 negative, ki-67 > 14%), *luminal B/HER2-positive-like* subtype (HR positive, HER2 positive), *HER2-positive-like* subtype (HR negative, HER2 positive) and *triple negative* subtype (HR negative, HER2 negative).

Chemotherapeutic and MRI protocols

The treatment plan was chosen by oncologists and explained to every patient. The initial evaluation of patients before NAC included a complete medical history, physical examination, complete blood work, chest X-ray, CT scan and bone scan. Clip titanium was placed in the tumour bed in all patients before starting chemotherapy, to identify the area of the primary tumour at the time of surgery. All patients with *HER2-positive* cancers received trastuzumab-based regimen as neoadjuvant therapy.

Tumour size was measured on the last MRI performed after completing NAC. The studies were done on a 1.5 T MRI scanner (Best, The Netherlands). The patient was placed in a prone position. Protocol in space-occupying lesions in the breast includes an axial T1-weighted sequence (TR: 494 msec, TE: 8 msec, number of acquired signals: 2, slice thickness: 3 mm, interval: 0.3 mm) and T2-weighted sequence (TR: 5000 msec, TE: 120 msec, number of acquired signals: 2, slice thickness: 3 mm, interval: 0.3 mm), followed by 3D T1-weighted fast spoiled gradient-echo dynamic sequence, selective excitation of water, (TR: 23 msec, TE: 5.7 msec, angle: 20º, slice thickness: 2 mm) acquiring 6 series, one pre-contrast series and five consecutive post-contrast series at 90-second intervals. Contrast agent (Gd-DOTA, DOTAREM, Guerbet) was administered using a bolus injection (2 mL/s) at a dose of 0.1 mmol/kg followed by a bolus of saline solution (20 mL). All images are analysed at a workstation. Subtraction images between the without contrast stage and the 2nd-3rd-4th-5th post-contrast phase were obtained, which were interpreted with the help of specific programs for the analysis of contrast enhancement and time-signal intensity curves.

MRI assessment

Assessment of response was based on changes in tumour size in the MRI contrast sequences. Tumour size was calculated by summing the maximum diameters of tumour enhancement on axial slices of MRI, as the Response Evaluation Criteria in Solid Tumours (RECIST). The absence of a clear enhancement indicates no residual cancer. The final response was defined as the change in size between the pre-treatment and post-treatment MRI. Response categories, based on radiological examination with contrast MRI, were classified as: (1) imaging complete response on MRI (iCR: no evidence of residual disease on posttreatment MRI); and (2) non-iCR: residual disease on posttreatment MRI.

Histopathologic analysis

Pathologic measurement of the tumour size was used as the "gold standard" and compared to the MRI-measured residual tumour size. Samples for histopathological examination were cut into 5 mm slices, fixed in 10 % neutral-buffered formalin, trying to identify any lesion that corresponded with invasive carcinoma. If the tumour lesion was evident, it was included in its entirety for morphological study with hematoxylin and eosin (H&E). If no evident tumour was found, the clip marker was identified, and slides from the block containing the marker as well as the adjacent blocks were examined. Tumour response after NAC was classified as (1) pCR: no residual invasive tumour in the breast on final pathology; and (2) non-pCR: presence of residual invasive cancer on final pathology. If any residual invasive disease, pathologic tumour size was determined by measuring the longest dimension of a sample stained with H&E and the number of blocks in which invasive tumour was detected.

Statistical analysis

A descriptive analysis of the variables included in the study was performed. Continuous variables were expressed as mean and standard deviation, and categorical variables were expressed as absolute values and percentages with their estimated 95% confidence interval. Comparison of means was performed using Student's t test or Mann-Whitney test and analysis of variance or Kruskal-Wallis test, as appropriate after checking normality with the Kolmogorov-Smirnov test. Association of qualitative variables was estimated using the Chi-square test. Pearson correlation analysis was used to compare the MRI-measured and pathological tumour sizes. Linear regression model was used to analyse the diagnostic accuracy of MRI. $P \leq 0.05$ was considered significant. Basic statistical indicators to assess the accuracy of MRI in detecting residual disease after NAC were calculated. The efficacy of MRI was measured by the predictive values. True negative (TN) was defined as negative in both MRI and pathology; true positive (TP) was defined as positive in both MRI and pathology; false negative (FN) was defined as negative on MRI and positive on pathology; and false positive (FP) was defined as positive on MRI and negative on pathology. To assess the accuracy of MRI in detecting residual disease, sensitivity: TP / (TP + FN), specificity: TN / (TN + FP), positive predictive value (PPV): TP / (TP + FP), negative predictive value (NPV): TN / (TN + FN), and overall accuracy: (VN + VP) / (TP +

TABLE 1. Clinical and tumour characteristics

CONTINUOUS VARIABLES		Mean	SD	Median	Range
AGE (years)		47.22	10.10	42.0	31.0-75.0
BASAL TUMOR SIZE (cm)		3.99	1.97	3.40	1.60-13.0
CATEGORICAL VARIABLES			**n**	**%**	**95% CI**
CLINICAL TUMOR STAGE	T1		7	7.6	1.6-13.6
	T2		69	75.0	65.6-84.4
	T3		13	14.1	6.5-21.8
	T4		3	3.3	0.7-9.2
HISTOLOGICAL TYPE	Ductal		85	92.4	86.4-98.4
	Lobular		7	7.6	1.6-13.6
HISTOLÓGICAL GRADE	G1		9	10.0	3.2-16.8
	G2		32	35.6	25.1-46.0
	G3		49	54.4	43.6-65.3
	NA		2		
HORMONAL RECEPTOR STATUS	Positive		60	65.2	54.9-75.5
	Negative		32	34.8	24.5-45.1
HER2 STATUS	Positive		25	27.2	17.5-36.8
	Negative		67	72.8	63.2-82.5
MOLECULAR SUBTYPE	Luminal A		11	12.0	4.8-19.1
	Luminal B/HER2-		35	38.0	27.6-48.5
	Luminal B/HER2+		16	17.4	9.1-25.7
	HER2+		9	9.8	3.2-16.4
	Triple negative		21	22.8	13.7-31.9
PRE-NAC AXILLARY STATUS	Positive		76	82.6	74.3-90.9
	Negative		16	17.4	9.1-25.7

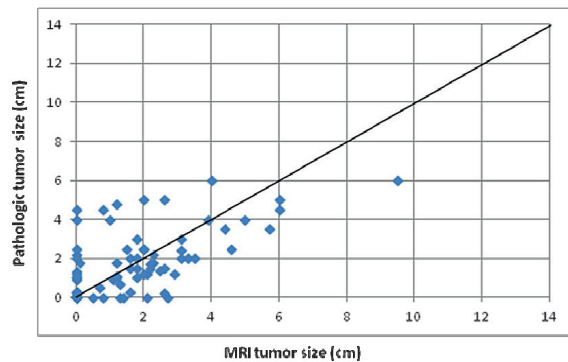CI = confidence interval; NA = not available; SD = standard deviation

FIGURE 1. Dispersion graph of the correlation between residual tumour sizes (cm) calculated at preoperative MRI (on the X-axis) and at pathological examination (on the Y-axis). Each point represents a tumour; if the pairs of data coincide, the points overlap. The bisector corresponds to the equivalence line. On the graph, the closer the points are to the equivalence line, the greater the correlation between MRI and pathology.

TABLE 2. MRI diagnostic performance in predicting pathologic response

		Pathology		Total
		No pCR	pCR	
MRI	No iCR	TP = 48	FP = 6	54 (58.70%)
	iCR	FN =16	TN = 22	38 (41.30%)
Total		64 (69.60%)	28 (30.40%)	92 (100%)

FN = false negative; FP = false positive; iCR = imaging complete response; pCR = pathologic complete response; TN = true negative; TP = true positive

TN + FP + FN) were calculated. Analyses were performed using IBM SPSS Statistics version 19.

Results

92 invasive breast tumours were analysed (1 patient with bilateral breast cancer was recorded). Initial clinicopathologic characteristics of patients and tumours of the study are shown in Table 1. Patients age ranged between 31 and 75 years (mean 47.22 years). Mean baseline tumour size determined by MRI was 3.99 cm. Most tumours were diagnosed as T2 stage (75%) and grade 3 (53.3%). The initial biopsy of the lesions revealed 85 cases of invasive ductal carcinoma and 7 cases of invasive lobular carcinoma. 11 tumours were classified as *luminal A*, 35 as *luminal B/HER2-*, 16 as *luminal B/HER2+*, 9 as *HER2+* and 21 as *triple negative*. Most patients (65.9%) received taxane-anthracycline based chemotherapy; *HER2-positive* patients (27.5%) were treated with a trastuzumab-based regimen. After NAC, mastectomy was performed in 21 cases (21.8%) and BCS was attempted in 71 cases (77.2%). Of the latter group, 16 cases were re-operated because tumour involvement or proximity to the resection margins.

Accuracy of MRI to detect residual disease after NAC

Tumour responses to NAC were compared based on the results obtained by MRI and pathological examination. MRI showed complete remission in

38 cases (41.3%) and residual disease in 54 cases (58.7%). The pathological study showed a pCR in 28 cases (30.4%) and invasive residual tumour was found in 64 samples (69.6%).The diagnostic performance of MRI for detecting residual tumour is summarized in Table 2. The sensitivity of MRI for detecting residual disease after NAC was 75% (48/64) and the specificity was 78.57% (22/28). The PPV (accuracy of MRI for detecting residual disease) was 88.89% (48/54). The NPV (accuracy of MRI in predicting pCR) was 57.89% (22/38). The overall accuracy of MRI was 76.09% (70/92). MRI showed FN diagnoses in 25% cases (16/64).

Accuracy of MRI to predict the residual tumour size after NAC

It was possible to compare the residual tumour size determined by MRI and pathological examination in 89 of the 92 cases of the study. In 3 cases it was not possible to determine the pathologic tumour size due to the presence of scattered residual multifocal disease. The mean residual tumour size determined by MRI after NAC was 1.44 cm. The final pathologic tumour size was 1.53 cm. The two measurements are correlated forwardly significantly (r = 0.648, p < 0.001) (Figure 1). The mean discrepancy between the two measures was 0.96 cm. The discrepancy was less than 1 cm in 57 cases (64.04%).

Analysis of factors influencing the accuracy of MRI for predicting residual tumour size.

Linear regression models were performed to find clinicopathological predictors of the diagnostic accuracy of MRI based on the absolute difference between the MRI-measured and pathologic residual tumour size (Table 3). The strongest predictor was tumour grade (p < 0.001). The mean absolute
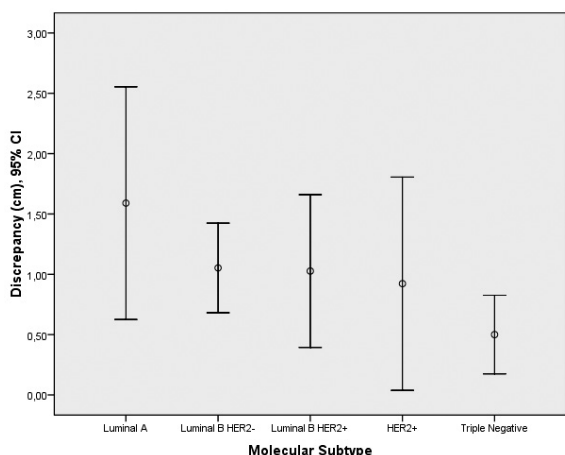
Discrepancy (cm) based on molecular subtypes [Mean±SD]: luminal A [1.59±1.34]; luminal B/HER2– [1.05±1.06]; luminal B/HER2+ [1.02±1.14]; luminal HER2+[0.92±1.14]; triple negative [0.50±0.70]

FIGURE 2. Discrepancy between MRI-measured and pathologic residual tumour size, based on molecular subtypes.

TABLE 3. Factors affecting the MRI diagnostic accuracy based on the discrepancy between MRI and pathologic residual tumour size

Variable	No.	Discrepancy (mean ± SD)	p-value
Age (years)			0.281
≤45	43	1.09 ±1.14	
>45	46	0.84 ±1.01	
Baseline tumour size (cm)			0.050
≤5	74	0.85 ±0.99	
>5	15	1.53 ±1.33	
Histological type			0.818
ductal	83	0.97 ±1.09	
lobular	6	0.87 ±0.82	
Histological grade			<0.001
1 or 2	40	1.44 ±1.24	
3	47	0.56 ±0.71	
Hormonal receptor status			0.033
positive	59	1.14 ±1.13	
negative	30	0.63 ±0.87	
HER2 status			0.906
positive	24	0.99 ±1.12	
negative	65	0.96 ±1.07	
Molecular subtype			0.055
Luminal A	10	1.59 ±1.34	
Luminal B-HER2-	34	1.05 ±1.06	
Luminal B-HER2+	15	1.02 ±1.14	
HER2+	9	0.92 ±1.14	
Triple negative	21	0.50 ±0.70	

SD = standard deviation

discrepancy was significantly lower in the group of high-grade tumours. In addition, the HR status was associated significantly with the diagnostic accuracy of MRI, observing a lower discrepancy in the group of *non-luminal* tumours (p = 0.033). Baseline tumour size was kept in the limit of significance, with a lower discrepancy in the group with baseline tumour size ≤ 5 cm. The age, histological type and HER2 status were not associated with the diagnostic accuracy of MRI. *Triple negative* subtype showed the smallest difference between the two measurements (Figure 2), although no statistically significant difference regarding the molecular phenotype of the tumour (p = 0.055). After a multivariate linear regression analysis, tumour grade (p = 0.001) and baseline tumour size (p = 0.030) remained significant independent predictors of MRI accuracy (Table 4).

Discussion

Several researchers have previously studied the diagnostic accuracy of MRI in detecting invasive breast carcinoma in patients undergoing NAC[31-34]; however, an accurate determination of residual tumour size is necessary to perform an optimal surgery and achieve negative margins. We conducted a comparative analysis of post-NAC MRI and pathological findings to describe the diagnostic accuracy of MRI to detect residual invasive disease and to estimate the residual tumour size after NAC. In the current study, the overall diagnostic

TABLE 4. Results from the Multivariate Regression Analysis

Variable	Regression coefficient (B)	se	p	95% CI
Tumour grade	0.807	0.236	0.001	0.338-1.276
HR status	0.086	0.249	0.729	-0.408-0.581
BTS (MRI)	0.610	0.277	0.030	0.060-1.161

BTS = baseline tumour size; CI = confidence interval; se = standard error

accuracy of MRI for detecting residual invasive carcinoma in the breast was 76.09%. The PPV and NPV were 88.89% and 57.89%, respectively. These data suggest that breast MRI is an accurate tool for assessing tumour response after NAC, although it is more limited in predicting pCR, which may be due to the NAC antiangiogenic effect in the tumour bed.

Correlation coefficients of residual tumour size assessed by MRI and pathology were considered good. Lobbes *et al.*[35] reviewed 17 studies comparing MRI-measured and pathologic residual tumour size. In this review, the mean correlation coefficient was 0.698. In our series, the value of the correlation coefficient was 0.648, reflecting a moderate correlation. If we remove the *luminal A-like* cases from

the calculation, in which it has been observed that NAC is not the optimal therapeutic strategy, the value of global correlation coefficient rises to 0.706 (p < 0.001). Although correlation coefficients provide important information about the MRI´s ability to assess response to NAC, the determination of the absolute difference between MRI-measured and pathologic residual tumour size is necessary to evaluate the diagnostic accuracy of MRI. MRI overestimation of residual tumour size can increase the number of unnecessary mastectomies and alter the cosmetic outcome of BCS with wide resection margins, while MRI underestimation can increase the number of reoperations. In the current study, the mean discrepancy was 0.96 cm. Less than 1 cm difference in the calculation of residual tumour size between MRI and pathology was observed in 57 tumours (64.04%). Identifying factors that may affect the accuracy of MRI for predicting residual tumour size could help to interpret breast MRI findings. Three recent studies evaluated the accuracy of MRI to predict residual tumour size after NAC and investigated the factors that influence the accuracy of MRI. In a study conducted by Ko et al.[36], the Pearson´s correlation coefficient between the tumour sizes measured using MRI and pathology was 0.749 (p < 0.001) and the mean of size discrepancy was 1.26 cm. According to the molecular subtype, tumour grade and tumour morphology on initial MRI, statistically significant differences of size discrepancy between both measurements were observed. Triple negative subtypes were measured more accurately (mean, size discrepancy = 0.8 cm). In the study by Chen et al.[37], the mean discrepancy was 1.0 cm, and predictive factors found in the univariate analysis were histological type, tumour morphology, HR status, HER2 status and type of MRI. Multivariate analysis identified as independent predictors histological type, tumour morphology and the combination of HER2-HR status. Finally, in a study by Moon et al.[38], the Pearson´s correlation coefficient and the mean difference between MRI-measured and pathologic tumour size was 0.664 (p < 0.001) and 1.39 cm, respectively. The clinicopathological factors associated with MRI accuracy were the initial T stage, the age at the time of the diagnosis and the ER expression status. In addition, Moon et al observed increased accuracy of MRI in predicting the residual tumour extent after NAC in triple negative breast cancer. In our study, a statistically significant association was observed between the absolute discrepancy and each of covariates: baseline tumour size, tumour grade and HR status. A minor discrepancy was observed

in tumours with an initial size ≤ 5 cm, in high-grade tumours and in non-luminal tumours. Despite a statistically significant association between molecular subtypes and the diagnostic accuracy of MRI was not observed (p = 0.055), a tendency to find better accuracy in triple negative tumours was found. The mean discrepancy in residual tumour size was lower in the group of triple negative tumours (0.50 cm). Multivariate analysis identified only as independent predictors baseline tumour size and tumour grade.

There are two important limitations to note in our study. The absence of ductal carcinoma in situ (DCIS) was not included in the definition of pCR, which can affect the accuracy of MRI. In addition, the current molecular classification includes a cut-off value of ki-67 expression level at 20% to define low or high level.[39]

Conclusions

In conclusion, MRI can accurately measure tumour response and residual tumour size in breast cancer patients treated with NAC. Both overestimation and underestimation of MRI-measured residual tumour size may cause an incorrect surgical planning so it´s important to consider the clinicopathological factors that can affect the diagnostic accuracy of breast MRI. In our series, evaluation of residual tumour size was more accurate in baseline tumour size ≤ 5 cm lesions, in high tumour grade lesions and in non-luminal breast cancer.

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